



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : C08F 220/06, 228/02, 236/02 G02C 7/04	A1	(11) International Publication Number: WO 92/11301 (43) International Publication Date: 9 July 1992 (09.07.92)
(21) International Application Number: PCT/US91/09625 (22) International Filing Date: 20 December 1991 (20.12.91) (30) Priority data: 632,467 21 December 1990 (21.12.90) US (71) Applicant: ALLERGAN, INC. [US/US]; 2525 DuPont Drive, Irvine, CA 92713-9534 (US). (72) Inventors: SULC, Jiri ; 503 Adams Street, Centerport, NY 11721 (US). KRCOVA, Zuzana ; 510 Fifth Avenue, East Northport, NY 11731 (US). CHEN, Patrick ; 98 George Avenue, Edison, NJ 08820 (US). BAO, Qi-Bin ; 30 Washington Court, Livingston, NJ 07039 (US).		(74) Agents: DILWORTH, Peter, G. et al.; Dilworth & Barrese, 333 Earle Ovington Boulevard, Uniondale, NY 11553 (US). (81) Designated States: AT (European patent), BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, LU (European patent), MC (European patent), NL (European patent), SE (European patent). Published <i>With international search report.</i>
(54) Title: BALANCED CHARGE POLYMER AND HYDROPHILIC CONTACT LENS MANUFACTURED THEREFROM (57) Abstract A water swellable crosslinked polymer of essentially balanced charge is obtained by polymerizing a polymer-forming composition comprising a cationic-anionic pair of ethylenically unsaturated monomers and a non-ionic ethylenically unsaturated hydrophilic and/or hydrophobic monomer. Contact lenses formed from the polymer exhibit little if any tendency to attract soils, e.g., proteinaceous debris, to their surfaces.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	ES	Spain	MG	Madagascar
AU	Australia	FI	Finland	ML	Mali
BB	Barbados	FR	France	MN	Mongolia
BE	Belgium	GA	Gabon	MR	Mauritania
BF	Burkina Faso	GB	United Kingdom	MW	Malawi
BG	Bulgaria	GN	Guinea	NL	Netherlands
BJ	Benin	GR	Greece	NO	Norway
BR	Brazil	HU	Hungary	PL	Poland
CA	Canada	IT	Italy	RO	Romania
CF	Central African Republic	JP	Japan	SD	Sudan
CG	Congo	KP	Democratic People's Republic of Korea	SE	Sweden
CH	Switzerland	KR	Republic of Korea	SN	Senegal
CI	Côte d'Ivoire	LI	Liechtenstein	SU ⁺	Soviet Union
CM	Cameroon	LK	Sri Lanka	TD	Chad
CS	Czechoslovakia	LU	Luxembourg	TG	Togo
DE*	Germany	MC	Monaco	US	United States of America
DK	Denmark				

+ Any designation of "SU" has effect in the Russian Federation. It is not yet known whether any such designation has effect in other States of the former Soviet Union.

BALANCED CHARGE POLYMER AND HYDROPHILIC
CONTACT LENS MANUFACTURED THEREFROM

1

BACKGROUND OF THE INVENTION

5 This invention relates to a polymer of essentially balanced charge which is obtained from the polymerization of a cationic-anionic monomer pair and a neutral comonomer and to a hydrophilic contact lens fabricated from the polymer.

Hydrophilic contact lenses are generally formed from covalently crosslinked polymers which are based on hydrophilic derivatives of acrylic or methacrylic acid, e.g., their hydrophilic esters or amides, hydrophilic vinylic polymers such as vinylpyrrolidone, and the like. In their hydrated state, these polymers are referred to as hydrogels, coherent three-dimensional polymer structures or net-works which are capable of absorbing large quantities of water without dissolving and of transporting oxygen. In addition to the hydrophilic monomer(s), the preparation of hydrogels used in the manufacture of contact lenses also utilizes minor amounts of less hydrophilic, and even hydrophobic, monomer(s) to confer mechanical strength and other useful properties.

One of the troublesome aspects of known types of hydrogel contact lenses lies in their tendency to accumulate various soils contained in tears, e.g., proteins, lipids, mucoids, etc., on their surfaces. The explanation for this tendency is not all that certain but is believed to be due to the interaction of the charged groups present on the soil components and the charge associated with the hydrogel. For instance, it is known that lysozyme, an enzyme present in tears, possesses a net positive charge and forms complexes with polymers such as the known types of hydrogels which

1 possess a net negative charge. This interaction of hydrogel
polymer surface and soil represents a significant
disadvantage for contact lenses manufactured therefrom.

5 In an effort to counteract this soil accumulation
tendency, U.S. Patent No. 4,569,858 proposes two methods for
treating a lens manufactured from an unhydrated polymer
having reactive groups, e.g., hydroxyl and/or acid groups,
on its surface with a compound which reacts with such groups
to provide a soil deposition-resistance hydrophobic coating,
10 hydrophilic coating or charged surface. In the first of the
two methods, the surface of the unhydrated lens is
pretreated with a dilute solution of a strong organic base
in a nonswelling solvent, e.g., potassium tert-butoxide in
ether, to convert surface hydroxyl groups to alkoxide groups
15 followed by reacting alkoxide and carboxylate groups with an
alkylating, acylating or sulfonating agent to provide a
hydrophobic surface. In the second method, the surface
hydroxyl and/or acid groups are directly reacted with a
reagent such as a diazoalkane to provide a soil deposition-
20 resistant surface.

In yet another approach to imparting soil
deposition-resistance to a hydrogel contact lens, U.S.
Patent No. 4,650,843 discloses forming the lens from a
monomeric composition containing 50-95 weight percent of a
25 monomethacrylate of an alkylene glycol, 5-35 weight percent
of at least one fluorine-containing monomer selected from
the group consisting of trifluoroethyl methacrylate,
hexafluorisopropyl methacrylate, pentafluoro-n-propyl
methacrylate and pentafluoro-n-butyl methacrylate, and less
30 than 40 weight percent of one or more compounds selected
from the group consisting of an unsaturated carboxylic acid

1 having one or more carboxyl groups in the molecule, a
monomethacrylate of a polyhydric alcohol having three or
more hydroxyl groups, and an alkyl methacrylate.

U.S. Patent No. 4,163,609 describes a contact lens
5 material, the surface of which is self-cleaning of organic
debris, by changing the surface charge from a natural
anionic positive charge which attracts debris to a cationic
negative charge which repels debris.

10 SUMMARY OF THE INVENTION

It is a principal object of the invention to
provide a polymer, suitable for the fabrication of a contact
lens, the surface of which possesses a substantially
balanced charge, and as such exhibits little if any tendency
15 to attract soils thereto.

It is a particular object of the invention to
provide such a balanced charge polymer by the polymerization
of a cationic-anionic monomer pair, e.g., an acidic monomer
such as acrylic acid and/or methacrylic acid and a basic
20 monomer such as diethylaminoethyl methacrylate, vinylamine,
aminostyrene and/or vinylpyrrolidine, and a non-ionic
comonomer, e.g., a hydrophilic comonomer such as
hydroxyethyl methacrylate (HEMA), hydroxypropyl
methacrylate, vinylpyrrolidone, glycerylmethacrylate,
25 acrylamide etc., and/or a hydrophobic comonomer such as
silicone-acrylate, silicone-alkylacrylate, silicone-
methacrylate, fluoromethacrylate, fluorosilicomethacrylate,
methylmethacrylate, etc.

It is another particular object of the invention
30 to provide a hydrophilic contact lens which has been
manufactured from the foregoing balanced charge polymer.

35

1 In keeping with these and other objects of the
invention, a polymer of essentially balanced charge is
provided which comprises the polymerizate derived from the
polymerization of a major amount of at least one cationic-
5 anionic pair of ethylenically unsaturated monomers and at
least one non-ionic ethylenically unsaturated monomer.

A hydrophilic contact lens fabricated from the
balanced charge polymer of this invention exhibits a
significantly reduced tendency to accumulate proteinaceous
10 materials, cell fragments and other soilants upon its
surface, a highly advantageous property compared with
contact lenses manufactured from the hydrogels exhibiting
some net surface charge.

15 DESCRIPTION OF THE PREFERRED EMBODIMENTS

The cationic-anionic monomer pair employed in the
polymerization of the balanced charge polymer of this
invention is made up of substantially equimolar amounts of
an ethylenically unsaturated cationic monomer, i.e., one
20 possessing one or more weakly or strongly acidic groups, and
an ethylenically unsaturated anionic monomer, i.e., one
possessing one or more weakly or strongly basic groups, the
positive and negative charges of the monomers being
substantially balanced in the pair. Strong acids and weak
25 acids can be regarded as those having pKa values of less
than about 2 and from about 2 to about 7, respectively, and
strong bases and weak bases can be regarded as those having
pKa values of greater than about 11 and from about 7 to
about 11, respectively.

30 Suitable cationic monomers include carboxylic
acids such as acrylic acid, methacrylic acid, itaconic acid,

1 maleic acid, 2-vinylpropionic acid and 4-vinylpropionic acid
and sulfonic acids such as methacroyloxypropylsulfonic acid,
vinylsulfonic acid and p-styrenesulfonic acid. Suitable
anionic monomers include the primary, secondary and tertiary
5 amines such as aminoethylmethacrylate, methylaminoethyl-
methacrylate, N,N-dimethylaminoethyl-methacrylate, N,N-
diethanolaminoethylmethacrylate, N,N-dimethoxyethylamino-
ethylmethacrylate, vinyl amine, aminostyrene, 2-vinyl
pyridine, 4-vinyl pyridine, morpholinomethacrylate and N-(2-
10 vinyloxyethyl) piperidine and quaternary ammonium compounds
such as 2-trimethylammoniummethyl methacrylic hydroxide, 2-
trimethylammoniumacrylic hydroxide, 2-trimethylammonium-
methyl methacrylic chloride, 2-trimethylammonium-
methylacrylic chloride, 2-methacroyloyloxyethyltrimethyl-
15 ammonium methyl sulfate and 2-hydroxy-3-methacroyloxy-
propyltrimethylammonium chloride.

Where the polymer is intended to be used for
manufacturing a contact lens, it is preferred that the
anionic-cationic monomer pair be either a conjugate of an
20 ethylenically unsaturated weak acid and an ethylenically
unsaturated weak base or an ethylenically unsaturated strong
acid and ethylenically unsaturated strong base. Where it is
not possible to form these conjugate monomer pairs by direct
reaction of the acid monomer with the base monomer, the
25 conjugates can usually be prepared from the salts of the
acids, e.g., the silver and barium salts, and the halides of
the bases, e.g., the chlorides, bromides and iodides, by
means of the disproportionation reaction.

While cationic-anionic monomer pairs based on
30 conjugates of a strong acid and a weak base or conjugates of
a weak acid and a strong base can be used, the dimensional

1 stability of the resulting hydrogel may be more sensitive to
changes in Ph than might be desirable for some applications,
particularly, contact lenses. However, for applications
where dimensional stability is not important, e.g., drug
5 delivery compositions, such monomer pairs are entirely
suitable.

Included within the expression "cationic-anionic
monomer pair" or its equivalent "conjugate monomer pair" as
used herein are ethylenically unsaturated internal salts
10 containing positive and negative charges substantially in
balance with each other. Examples of these internal
monomeric salts which can be used herein as the cationic-
anionic monomer pair are N-(3-sulfopropyl)-methacroy-
loxyethyl-N,N-dimethylammonium-betain (SPE), N-(3-sulfo-
15 propyl)-N-methacrylamidopropyl-N,N-dimethylammonium-betain
(SPP), 1-(3-sulfopropyl)-2-vinyl-pyridinium-betain (SPV), N-
(3-carboxypropyl)-N-methylamino-methacryloyloxyethyl-N,N-
dimethylammonium-betain (CPE), N-(3-carboxypropyl)
aminoethylmethacrylate, 2-(methacryloyloxy)ethyl-2-
20 (trimethylammonium) ethylphosphate, etc.

Following its preparation, the cationic-anionic
monomer pair is combined with at least one ethylenically
unsaturated non-ionic monomer which can be hydrophilic,
e.g., 2-hydroxyethyl methacrylate (HEMA), hydroxy-
25 propylmethacrylate, vinylpyrrolidone, glycerylmethacrylate,
acrylamide, etc., or hydrophobic, e.g., silicone-acrylate,
silicone-alkylacrylate, silicone-alkylmethacrylate,
fluoromethacrylate, fluorosilico-methacrylate, etc. The
amount of non-ionic monomer(s) can vary from about 1 to
30 about 99.5, and preferably from about 50 to about 95, weight
percent of the total weight of monomer present in the

1 polymer-forming composition. Where the polymer-forming
composition contains only hydrophilic non-ionic monomer(s),
the amount of such monomer(s) can vary from about 50 to
about 99.5, and preferably from about 65 to about 95, weight
5 percent of the total monomer content. Where the polymer-
forming composition contains only hydrophobic non-ionic
monomer(s), the amount of such monomers can vary from about
0.5 to about 80, and preferably from about 1 to about 60,
weight percent of the total monomer content. Combinations
10 of hydrophilic and hydrophobic monomers over a wide range of
weight ratios can be utilized to impart a variety of
mechanical and/or water swellability performance
characteristics.

The order of addition of the monomer components to
15 the polymer-forming composition is generally not critical.
However, it is preferred to combine both components of the
cationic-anionic monomer pair before adding any of the other
ingredients of the polymerization medium since this will
provide better control over the balanced conjugate-forming
20 operation.

The foregoing monomer mixture can also contain a
crosslinking monomer containing at least two ethylenic
sites. Examples of such crosslinking monomers include
ethylene glycol dimethacrylate (EGDMA) and diacrylate,
25 diethyleneglycol dimethacrylate and diacrylate,
triethyleneglycol dimethacrylate and diacrylate, 1,3-
propanediol dimethacrylate and diacrylate, 2,2-
dimethylpropanediol diacrylate, tripropylene glycol
dimethacrylate and diacrylate, 1,3-butylene glycol
30 dimethacrylate and diacrylate, divinylbenzene, sorbitol
dimethacrylate, bis-acrylamide, etc. In general, the

1 crosslinking monomer can be present at a level of from about
0.01 to about 5, and preferably from about 0.2 to about 2,
weight percent of the total weight of monomers present in
the polymer-forming mixture.

5 In lieu of crosslinking monomer, covalent
crosslinking of the non-hydrated polymer of this invention
can be achieved by other means, e.g., by heating the polymer
prior to hydration, e.g., at 100-150°C, so that ionic bonds
in at least some carboxyl-amine conjugates are converted to
10 aminidic bonds. Crosslinking can also be achieved by
irradiating the non-hydrated polymer, e.g., at from 0.1 to
1.0 megarads. As those skilled in the art recognize,
whichever of these methods is used the degree of
crosslinking must be sufficient to render the polymer water
15 soluble yet water swellable.

Polymerization of the monomer mixture should be
carried out in the absence of water. However, the monomer
mixture can be diluted with suitable non-aqueous solvents,
e.g., glycerine, ethylene glycol, propylene glycol,
20 diacetin, acetic acid, dimethylsulfoxide, dimethylformamide,
the cellosolves, etc., to control volume changes during
xerogel lens swelling. The monomer mixture including any
other ingredients such as crosslinking monomer, peroxide
initiator, etc., can be polymerized to provide the balanced
25 charge polymer of this invention employing known and
conventional techniques. The polymer can be formed in situ
in a suitable mold via the spin casting procedure to provide
a hydrophilic contact lens. Suitable spin casting apparatus
and techniques are disclosed, inter alia, in U.S. Patent
30 Nos. 3,660,545, 4,468,184, 4,516,924, 4,517,138, 4,517,139,
4,517,140 and 4,680,149, the contents of which are

1 incorporated by reference herein. The polymer can also be
formed in situ in a two-piece lens mold to provide the
desired lens shape. Alternatively, a contact lens can be
5 obtained by lathing a lens blank fabricated from the
balanced charge polymer to the appropriate configuration.

In addition to contact lenses, the balanced charge
polymer of this invention can be used to prepare implantable
prostheses, e.g., intra-corneal implants, intra-ocular
lenses, etc., drug delivery systems, and the like.

10 The following examples are illustrative of the
balanced charge polymer of this invention and contact lenses
fabricated therefrom.

15

20

25

30

35

1

EXAMPLE 1

This example compares the surface soiling characteristics of two contact lenses, Lenses A and B, prepared by molding in a two-piece plastic lens mold a polymer obtained in accordance with this invention (Lens A) and a known polymer (Lens B).

The polymer-forming compositions were formulated as follows:

Lens A

10	<u>Component</u>	<u>Weight %</u>
	N,N-Dimethylaminoethyl methacrylate	5.678
	Methacrylic acid (MAA)	2.822
	2-Hydroxyethyl methacrylate (HEMA)	76.075
	Ethylene glycol dimethacrylate (EGDMA)	0.425
15	Ethylene glycol	15.0

Lens B

	<u>Component</u>	
	MAA	1.5
	HEMA	83.0
20	EGDMA	0.5
	Glycerine	15

To each of these compositions was added 0.5 weight percent of azobisdimethylvaleronitrile initiator. A quantity of each polymer-forming composition was placed in a two-piece plastic lens mold where polymerization was carried out under nitrogen at 80°C for 5 hours to provide the contact lens which was then hydrated in isotonic saline solution.

The 24 hour assay procedure whereby the hydrated lenses were measured for their tendency to attract protein, specifically lysozyme, to their surfaces was as follows:

35

1 Each lens was incubated at 35°C in a Ph 7.4
buffered isotonic saline solution containing 1.2 mg
lysozyme/ml. After 24 hours of incubation, the lenses were
rinsed with buffered saline and their ultraviolet
5 absorbances were measured spectrophotometrically. Protein
deposition was calculated using an extinction coefficient of
2.38 cm³/mg at 280 nm.

 In addition to the foregoing protein deposition
assay, Lenses A and B were compared for pH sensitivity,
10 tensile strength (g/mm²) and ionic charge sensitivity. The
results of all three testing procedures were as follows:

	<u>Property</u>	<u>Lens A</u>	<u>Lens B</u>
15	Retention of Lysozyme on the Lens Surface	0.03 mg/lens (estimated)	0.33 mg/lens
	pH Sensitivity	Not sensitive to pH 3.5-8.5; lens expounds 6% at pH 9 and expands 3% at pH 3.5.	Sensitive to different levels of pH; lens shrinks 10% at pH 4.
20	Tensile Strength (g/mm ²)	70	80
25	Ionic charge sensitivity	Not Sensitive; water content changes 2% between saline and deion- ized water	Very sensitive; water content changes 15% between saline and deionized water

 In addition to the dramatically reduced retention of
lysozyme on its surfaces, Lens A exhibited greater
biocompatibility, higher water affinity, reduced dehydration
30 and greater wearer comfort than Lens B.

EXAMPLE 2

90 Weight parts of HEMA containing 0.4 weight percent of EGDMA was mixed with 10 weight parts of monomer charge-conjugate prepared in the following manner:

1 Mole of methacrylic acid was slowly added to 1 mole of dimethylaminoethyl methacrylate under intensive cooling and stirring so that the temperature would not exceed 30°C. The conjugate was recrystallized from methanol solution. 0.1 Weight percent of azobisisobutyronitrile initiator was added to the monomer mixture which was then polymerized at 60°C under nitrogen in a two-piece plastic mold. After 2 hours the mold was opened and the finished lens hydrated in isotonic saline solution. The liquid content of the lens was 55 weight percent.

EXAMPLE 3

The azobisisobutyronitrile initiator in the polymer-forming mixture of Example 2 was replaced with benzoin methylether and the mixture was polymerized by spincasting with UV irradiation (at 365 nm; 60 W Hg lamp at 5.0 cm distance for 20 minutes). The resulting lens had similar properties as the lens of Example 2.

EXAMPLE 4

50 Weight parts of ethyltriglycolmethacrylate, 50 weight parts of the monomer conjugate of Example 2 and 2 weight parts of EGDMA were mixed. Polymerization of the mixture was initiated with 0.5% of azobisdimethylvaleronitrile in a two-piece plastic mold at 60°C for 3 hours and at 80°C for 2 hours. The resulting lens contained 71 weight percent of water at equilibrium hydration in saline.

1

EXAMPLE 5

50 Grams of ethoxyethyl methacrylate were mixed with 50 grams of the monomer conjugate of Example 2 and 0.8 grams of EGDMA. The mixture was initiated by 0.08% of azobisisobutyronitrile and polymerized for 24 hours at 60°C in a sealed glass ampule. After cooling, the ampule was broken and the resulting polymer block was lathed and polished into a lens. The resulting lens contained 80 weight percent water after complete hydration in isotonic saline solution.

10

EXAMPLE 6

A mixture of 20 weight parts of 3-methacryloxypropyltris(trimethylsiloxy)silane, 1 weight part of EGDMA and 80 weight parts of the monomer conjugate of Example 2 was diluted with 10% of Cellosolve. 0.1 Weight percent of azobisisobutyronitrile was added and the mixture was polymerized in a plastic two-piece plastic mold at 80°C for 3 hours. The resulting lens contained 60 weight percent water after complete hydration in saline, an oxygen permeability of $DK=35-40 \times 10^{-11}$ (cm^2/sec) ($\text{ml O}_2/[\text{ml} \times \text{mmHg}]$) and a tensile strength in the hydrated state of 120g/mm².

20

EXAMPLE 7

30 Weight parts of n-hexyl methacrylate, 0.5 weight parts of EGDMA and 70 weight parts of the monomer conjugate of Example 2 were mixed. The mixture was initiated by 0.1 weight percent of azobisisobutyronitrile and polymerized 4 hours at 60°C in a two-piece plastic mold. The resulting lens contained 70 weight percent water after complete hydration in saline and exhibited a tensile strength in the hydrated state of 110g/mm².

30

35

1

EXAMPLE 8

30 Grams of ethylmethacrylate were mixed with 7
grams of the monomer conjugate of Example 2 and 0.5 grams of
EGDMA. The mixture was initiated by 0.1 grams
5 azobisisobutyronitrile and polymerized in a two-piece plastic
mold at 80°C for 3 hours. The resulting lens contained 78
weight percent water after complete hydration in saline and a
tensile strength of 100 g/mm².

EXAMPLE 9

10 80 Weight percent parts of hydroxypropyl
methacrylate, 20 weight parts of the monomer conjugated from
Example 2 and 0.5 parts EGDMA were mixed. 0.1 Weight percent
azobisisobutyronitrile two-piece plastic mold was added and
the mixture was polymerized at 75°C for 4 hours. The
15 resulting lens contained 57 weight percent water after
complete hydration in saline, a tensile strength of 80 g/mm²
and an elongation in the hydrated state of 440%.

EXAMPLE 10

20 30 Grams of methyl methacrylate were mixed with 70
grams of the monomer conjugate of Example 2 together with 0.5
grams EGDMA. Polymerization was initiated by 0.08% weight
percent of azobisisobutyronitrile for 24 hours at 60°C in a
sealed glass ampule. After cooling, the ampule was broken and
the resulting polymer block was lathed and polished into a
25 lens. The resulting lens contained 70 weight percent water
after complete hydration in isotonic saline.

30

35

1

EXAMPLE 11

3 Weight parts of tertiary-butylmethacrylate, 0.05 weight parts of EGDMA and 7 weight parts of the monomer conjugate of Example 2 were mixed. The mixture was initiated with 0.5% azobisdimethylvaleronitrile and polymerized in a two-piece plastic mold at 60°C for 3 hours. The resulting lens contained 77 weight percent water after hydration in saline and a tensile strength in the hydrated state of 80 g/mm².

10

EXAMPLE 12

3 Weight parts of n-butylmethacrylate, 7 weight parts of the monomer conjugate of Example 2 and 0.05 weight parts of EGDMA were mixed. The mixture was initiated with 0.5% azobisdimethylvaleronitrile and polymerized in a two-part plastic mold at 60°C for 4 hours. The resulting lens contained 70 weight percent water after complete hydration in saline.

15

EXAMPLE 13

3 Weight parts of tetrafluoropropylmethacrylate, 7 weight parts of the monomer conjugate of Example 2 and 0.05 weight of EGDMA were mixed. Polymerization was initiated with azobisdimethylvaleronitrile in a two-piece plastic mold at 80°C for 3 hours. The resulting lens contained 70 weight percent water after complete hydration in saline.

25

30

35

EXAMPLE 14

1 Mole of methacrylic acid was slowly added to 1 mole dimethylaminoethylmethacrylamide and cooled below 20°C. 20 weight parts of the resulting conjugate were mixed with 80 weight parts of HEMA and 0.2 weight parts of EGDMA. Polymerization was initiated with 0.5 weight percent of azobisdimethylvaleronitrile in substantially the same manner as in Example 13. The resulting lens contained 69 weight percent water after complete full hydration in isotonic saline.

EXAMPLE 15

10 Weight parts of methacryloyloxypropyl sulfonic acid and methacryloyloxypropyl trimethylammonium base conjugate were dissolved in 90 weight parts of HEMA containing 0.5 weight percent of EGDMA. Polymerization of the mixture was initiated by 0.5 weight percent of azobisdimethylvaleronitrile in substantially the same manner as in Example 13. The resulting lens had 50% of water after complete hydration in isotonic saline solution.

EXAMPLE 16

10.1 Weight parts of SPE were dissolved in 15 weight parts of propyleneglycol and 74.4 weight parts of HEMA containing 0.5 weight percent EGDMA. Polymerization was initiated by 0.2 weight percent benzoinmethylether. A contact lens was manufactured from the polymer-forming mixture by the spincoating method employing photopolymerization. The resulting lens contained 52 weight percent water in isotonic saline solution.

1

EXAMPLE 17

A conjugate monomer pair was prepared by slowly combining 8.46g t-butylaminoethylmethacrylate (t-BAEMA) in 10g acetone with 4.3g methacrylic acid (MAA) in 10g acetone and thereafter cooling the combined material to below 5°C. The crude t-BAEMA-MAA conjugate pair was separated from the acetone by filtration, dried at ambient temperature under vacuum and recrystallized by dissolving 10g of the conjugate in 15g acetone at 35°C and placing the solution overnight in a refrigerator.

A contact lens was prepared by combining 1.6g HEMA, 0.4g t-BAEMA-MAA conjugate pair prepared as described, 0.01 azobisdimethylvaleronitrile and 0.35g propylene glycol (solvent), placing the polymer-forming composition in a two-piece plastic lens mold and polymerizing as in Example 1. The resulting contact lens swelled 55 weight percent in isotonic saline solution.

EXAMPLE 18

Following the procedures described in Example 17, a contact lens was prepared from a polymer-forming composition containing 1.7g hydroxypropylmethacrylate, 0.3 g N-methacryloyoxyethyl-N,N-dimethyl-N,2-ethyl carboxybetaine (CPE), 0.01 g EGDMA and 0.01g azobisdimethylvaleronitrile. The resulting contact lens was clear and swelled to 51 weight percent of water in isotonic saline solution.

30

35

1 WHAT IS CLAIMED IS:

1. A charge balanced, water swellable crosslinked polymer which comprises the polymerizate derived from the copolymerization of at least one cationic-anionic pair of
5 ethylenically unsaturated monomers and at least one non-ionic ethylenically unsaturated monomer.

2. The polymer of Claim 1 wherein the polymerizate is further derived from a crosslinking monomer containing at least two ethylenic sites.

10 3. The polymer of Claim 1 wherein the cationic-anionic pair is made up of a relatively weak monomeric acid and a relatively weak monomer base.

4. The polymer of Claim 3 wherein the relatively weak monomeric acid is a carboxylic acid and the relatively
15 weak base is a primary, secondary or tertiary amine.

5. The polymer of Claim 4 wherein the carboxylic acid is selected from the group consisting of acrylic acid, methacrylic acid, itaconic and, maleic acid, 2-vinylpropionic acid and 4-vinylpropionic acid and the primary, secondary or
20 tertiary amine is selected from aminoethylmethacrylate, methylaminoethylmethacrylate, N,N-dimethylaminoethylmethacrylate, N,N-diethanolaminoethylmethacrylate, N,N-dimethoxyethylaminoethylmethacrylate, vinyl amine, aminostyrene, 2-vinyl pyridine, 4-vinyl pyridine,
25 morpholinomethacrylate and N-(2-vinyloxyethyl) piperidine.

6. The polymer of Claim 1 wherein the cationic-anionic pair is made up of a relatively strong monomeric acid and a relatively strong monomeric base.

7. The polymer of Claim 6 wherein the relatively
30 strong monomeric acid is a sulfonic acid and the relatively strong base is a quaternary ammonium compound.

1 8. The polymer of Claim 7 wherein the sulfonic acid
is selected from the group consisting of methacroyoxypropyl-
sulfonic acid, vinylsulfonic acid and p-styrenesulfonic acid
and the quaternary ammonium compound is selected from the
5 group consisting of 2-trimethylammonium methyl methacrylic
hydroxide, 2-trimethylammonium-acrylic hydroxide, 2-
trimethylammonium methyl methacrylic chloride, 2-
trimethylammoniummethyl acrylic chloride, 2-methacryl-
oyloxyethyltrimethyl-ammonium methyl sulfate and 2-hydroxy-3-
10 methacroyoxypropyltrimethylammonium chloride.

9. The polymer of Claim 1 wherein the cationic-
anionic pair is made up of a relatively strong acid and a
relatively weak base.

10. The polymer of Claim 1 wherein the cationic-
15 anionic pan is made up of a relatively weak acid and a
relatively strong base.

11. The polymer of Claim 1 wherein the cationic-
anionic pair is provided as an internal monomeric salt.

12. The polymer of Claim 11 wherein the internal
20 monomeric salt is selected from the group consisting of
N-(3-sulfopropyl)-methacroyoxyethyl-N,N-dimethylammonium-
betain, N-(3-sulfo-propyl)-N-methacrylamidopropyl-N, N-
dimethylammonium-betain, 1-(3-sulfopropyl)-2-vinyl-pyridinium-
betain, N-methacryloyloxyethyl-N,N-dimethyl-N,2-ethyl
25 carboxybetaine (CPE), N-(3-carboxypropyl)-N-methylamino-
ethylmethacrylate, N-(3-carboxypropyl) aminoethylmethacrylate
and 2-(methacryloyloxy)ethyl-2-(trimethylammonium)
ethylphosphate.

13. The polymer of Claim 1 wherein the non-ionic
30 monomer is selected from the group consisting of 2-
hydroxyethyl methacrylate, hydroxypropylmethacrylate,

35

1 vinylpyrrolidone, glycerylmethacrylate, acrylamide, silicone-
acrylate, silicone-alkylacrylate, silicone-alkylmethacrylate,
fluoromethacrylate, fluorosilico-methacrylate and mixtures
thereof.

5 14. A hydrophilic contact lens manufactured from
the polymer of Claim 1.

15 15. A hydrophilic contact lens manufactured from
the polymer of Claim 2.

10 16. A hydrophilic contact lens manufactured from
the polymer of Claim 3.

17. A hydrophilic contact lens manufactured from
the polymer of Claim 4.

18. A hydrophilic contact lens manufactured from
the polymer of Claim 5.

15 19. A hydrophilic contact lens manufactured from
the polymer of Claim 6.

20. A hydrophilic contact lens manufactured from
the polymer of Claim 7.

20 21. A hydrophilic contact lens manufactured from
the polymer of Claim 8.

22. A hydrophilic contact lens manufactured from
the polymer of Claim 11.

23. A hydrophilic contact lens manufactured from
the polymer of Claim 12.

25 24. A hydrophilic contact lens manufactured from
the polymer of Claim 13.

30

35

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ¹		
According to International Patent Classification (IPC) or to both National Classification and IPC		
IPC (5): C08F 220/06, 228/02, 236/02; G02C 7/04		
U.S. CL. 526/265, 278, 287, 288, 310, 312; 351/160R, 160H		
II. FIELDS SEARCHED		
Minimum Documentation Searched ²		
Classification System	Classification Symbols	
U.S.	526/265, 278, 287, 288, 310, 312; 351/160R, 160H	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ³		
III. DOCUMENTS CONSIDERED TO BE RELEVANT ^{1,4}		
Category ⁵	Citation of Document, ^{1,6} with indication, where appropriate, of the relevant passages ^{1,7}	Relevant to Claim No. ^{1,8}
E, X	US, A, 5,075,399 (AHMED ET AL.) 24 DECEMBER 1991; See entire document.	1-24
Y	US, A, 4,666,964 (HUNTER ET AL.) 19 MAY 1987; See entire document.	1-24
Y	US, A, 4,251,651 (KAWAKAMI ET AL.) 17 FEBRUARY 1981; See entire document.	1-24
<p>¹ Special categories of cited documents: ^{1,5}</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"I" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search ¹		Date of Mailing of this International Search Report ¹
16 MARCH 1992		16 APR 1992
International Searching Authority ¹		Signature of Authorized Person ¹
ISA/US		Paul Michl Paul Michl

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE¹

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers _____, because they relate to subject matter ¹² not required to be searched by this Authority, namely:

2. ☐ Claim numbers _____, because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out ¹², specifically:

3. ☐ Claim numbers _____, because they are dependent claims not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☒ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING²

This International Searching Authority found multiple inventions in this international application as follows:

Group I: Claims 1-13 drawn to ampholytic polymer compositions, classified in Class 526, Subclass 287

Group II: Claims 14-24 drawn to lenses from polymer compositions of Group I, Classified in Class 351, Subclass 160R.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application. Telephone Practice

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
☐ No protest accompanied the payment of additional search fees.



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification⁵ : C08F 220/06, 228/02, 236/02 G02C 7/04	A1	(11) International Publication Number: WO 92/11301 (43) International Publication Date: 9 July 1992 (09.07.92)
(21) International Application Number: PCT/US91/09625 (22) International Filing Date: 20 December 1991 (20.12.91) (30) Priority data: 632,467 21 December 1990 (21.12.90) US (71) Applicant: ALLERGAN, INC. [US/US]; 2525 DuPont Drive, Irvine, CA 92713-9534 (US). (72) Inventors: SULC, Jiri ; 503 Adams Street, Centerport, NY 11721 (US). KRCOVA, Zuzana ; 510 Fifth Avenue, East Northport, NY 11731 (US). CHEN, Patrick ; 98 George Avenue, Edison, NJ 08820 (US). BAO, Qi-Bin ; 30 Washington Court, Livingston, NJ 07039 (US).		(74) Agents: DILWORTH, Peter, G. et al.; Dilworth & Barrese, 333 Earle Ovington Boulevard, Uniondale, NY 11553 (US). (81) Designated States: AT (European patent), BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, LU (European patent), MC (European patent), NL (European patent), SE (European patent). Published <i>With international search report.</i>
(54) Title: BALANCED CHARGE POLYMER AND HYDROPHILIC CONTACT LENS MANUFACTURED THEREFROM (57) Abstract A water swellable crosslinked polymer of essentially balanced charge is obtained by polymerizing a polymer-forming composition comprising a cationic-anionic pair of ethylenically unsaturated monomers and a non-ionic ethylenically unsaturated hydrophilic and/or hydrophobic monomer. Contact lenses formed from the polymer exhibit little if any tendency to attract soils, e.g., proteinaceous debris, to their surfaces.		

* (Referred to in PCT Gazette No. 23/1992, Section II)

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	ES	Spain	MG	Madagascar
AU	Australia	FI	Finland	ML	Mali
BB	Barbados	FR	France	MN	Mongolia
BE	Belgium	GA	Gabon	MR	Mauritania
BF	Burkina Faso	GB	United Kingdom	MW	Malawi
BG	Bulgaria	GN	Guinea	NL	Netherlands
BJ	Benin	GR	Greece	NO	Norway
BR	Brazil	HU	Hungary	PL	Poland
CA	Canada	IT	Italy	RO	Romania
CF	Central African Republic	JP	Japan	SD	Sudan
CG	Congo	KP	Democratic People's Republic of Korea	SE	Sweden
CH	Switzerland			SN	Senegal
CI	Côte d'Ivoire	KR	Republic of Korea	SU ⁺	Soviet Union
CM	Cameroon	LI	Liechtenstein	TD	Chad
CS	Czechoslovakia	LK	Sri Lanka	TC	Togo
DE*	Germany	LU	Luxembourg	US	United States of America
DK	Denmark	MC	Monaco		

⁺ Any designation of "SU" has effect in the Russian Federation. It is not yet known whether any such designation has effect in other States of the former Soviet Union.

1 BALANCED CHARGE POLYMER AND HYDROPHILIC
 CONTACT LENS MANUFACTURED THEREFROM

BACKGROUND OF THE INVENTION

5 This invention relates to a polymer of
essentially balanced charge which is obtained from the
polymerization of a cationic-anionic monomer pair and a
neutral comonomer and to a hydrophilic contact lens
fabricated from the polymer.

10 Hydrophilic contact lenses are generally formed
from covalently crosslinked polymers which are based on
hydrophilic derivatives of acrylic or methacrylic acid,
e.g., their hydrophilic esters or amides, hydrophilic
vinyllic polymers such as vinylpyrrolidone, and the like.
15 In their hydrated state, these polymers are referred to as
hydrogels, coherent three-dimensional polymer structures or
net-works which are capable of absorbing large quantities
of water without dissolving and of transporting oxygen. In
addition to the hydrophilic monomer(s), the preparation of
20 hydrogels used in the manufacture of contact lenses also
utilizes minor amounts of less hydrophilic, and even
hydrophobic, monomer(s) to confer mechanical strength and
other useful properties.

25 One of the troublesome aspects of known types of
hydrogel contact lenses lies in their tendency to
accumulate various soils contained in tears, e.g.,
proteins, lipids, mucoids, etc., on their surfaces. The
explanation for this tendency is not all that certain but
is believed to be due to the interaction of the charged
30 groups present on the soil components and the charge
associated with the hydrogel. For instance, it is known

35

1

-2-

5 that lysozyme, an enzyme present in tears, possesses a net positive charge and forms complexes with polymers such as the known types of hydrogels which possess a net negative charge. This interaction of hydrogel polymer surface and soil represents a significant disadvantage for contact
10 lenses manufactured therefrom.

In an effort to counteract this soil accumulation tendency, U.S. Patent No. 4,569,858 proposes two methods for treating a lens manufactured from an unhydrated polymer having reactive groups, e.g., hydroxyl and/or acid groups,
15 on its surface with a compound which reacts with such groups to provide a soil deposition-resistance hydrophobic coating, hydrophilic coating or charged surface. In the first of the two methods, the surface of the unhydrated lens is pretreated with a dilute solution of a strong
20 organic base in a nonswelling solvent, e.g., potassium tert-butoxide in ether, to convert surface hydroxyl groups to alkoxide groups followed by reacting alkoxide and carboxylate groups with an alkylating, acylating or sulfonating agent to provide a hydrophobic surface. In the
25 second method, the surface hydroxyl and/or acid groups are directly reacted with a reagent such as a diazoalkane to provide a soil deposition-resistant surface.

In yet another approach to imparting soil deposition-resistance to a hydrogel contact lens, U.S.
30 Patent No. 4,650,843 discloses forming the lens from a monomeric composition containing 50-95 weight percent of a

35

SUBSTITUTE SHEET

1

-3-

5 monomethacrylate of an alkylene glycol, 5-35 weight percent
of at least one fluorine-containing monomer selected from
the group consisting of trifluoroethyl methacrylate,
hexafluorisopropyl methacrylate, pentafluoro-n-propyl
methacrylate and pentafluoro-n-butyl methacrylate, and less
10 than 40 weight percent of one or more compounds selected
from the group consisting of an unsaturated carboxylic acid
having one or more carboxyl groups in the molecule, a
monomethacrylate of a polyhydric alcohol having three or
more hydroxyl groups, and an alkyl methacrylate.

15 U.S. Patent No. 4,163,609 describes a contact
lens material, the surface of which is self-cleaning of
organic debris, by changing the surface charge from a
natural anionic positive charge which attracts debris to a
cationic negative charge which repels debris.

20

SUMMARY OF THE INVENTION

It is a principal object of the invention to
provide a polymer, suitable for the fabrication of a
contact lens, the surface of which possesses a
25 substantially balanced charge, and as such exhibits little
if any tendency to attract soils thereto.

It is a particular object of the invention to
provide such a balanced charge polymer by the
polymerization of a cationic-anionic monomer pair, e.g., an
30 acidic monomer such as acrylic acid and/or methacrylic acid
and a basic monomer such as diethylaminoethyl methacrylate,

35

1

-4-

5 vinylamine, aminostyrene and/or vinylpyrrolidine, and a non-
ionic comonomer, e.g., a hydrophilic comonomer such as
hydroxyethyl methacrylate (HEMA), hydroxypropyl
methacrylate, vinylpyrrolidone, glycerylmethacrylate,
acrylamide etc., and/or a hydrophobic comonomer such as
10 silicone-acrylate, silicone-alkylacrylate, silicone-
methacrylate, fluoromethacrylate, fluorosilicomethacrylate,
methylemethacrylate, etc.

It is another particular object of the invention
to provide a hydrophilic contact lens which has been
15 manufactured from the foregoing balanced charge polymer.

In keeping with these and other objects of the
invention, a polymer of essentially balanced charge is
provided which comprises the polymerizate derived from the
polymerization of a major amount of at least one cationic-
20 anionic pair of ethylenically unsaturated monomers and at
least one non-ionic ethylenically unsaturated monomer.

A hydrophilic contact lens fabricated from the
balanced charge polymer of this invention exhibits a
significantly reduced tendency to accumulate proteinaceous
25 materials, cell fragments and other soilants upon its
surface, a highly advantageous property compared with
contact lenses manufactured from the hydrogels exhibiting
some net surface charge.

30

35

SUBSTITUTE SHEET

1

-5-

5 DESCRIPTION OF THE PREFERRED EMBODIMENTS

The cationic-anionic monomer pair employed in the polymerization of the balanced charge polymer of this invention is made up of substantially equimolar amounts of an ethylenically unsaturated cationic monomer, i.e., one
10 possessing one or more weakly or strongly acidic groups, and an ethylenically unsaturated anionic monomer, i.e., on possessing one or more weakly or strongly basic groups, the positive and negative charges of the monomers being substantially balanced in the pair. Strong acids and weak
15 acids can be regarded as those having pKa values of less than about 2 and from about 2 to about 7, respectively, and strong bases and weak bases can be regarded as those having pKa values of greater than about 11 and from about 7 to about 11, respectively.

20 Suitable cationic monomers include carboxylic acids such as acrylic acid, methacrylic acid, itaconic acid, maleic acid, 2-vinylpropionic acid and 4-vinylpropionic acid and sulfonic acids such as methacroyloxypropylsulfonic acid, vinylsulfonic acid and p-
25 styrenesulfonic acid. Suitable anionic monomers include the primary, secondary and tertiary amines such as aminoethylmethacrylate, methylaminoethyl-methacrylate, N,N-dimethylaminoethyl-methacrylate, N,N-diethanolaminoethylmethacrylate, N,N-dimethoxyethylamino-
30 ethylmethacrylate, vinyl amine, aminostyrene, 2-vinyl pyridine, 4-vinyl pyridine, morpholinomethacrylate and N-

35

SUBSTITUTE SHEET

1

-6-

- 5 (2-vinyloxyethyl) piperidine and quaternary ammonium compounds such as 2-trimethylammoniummethyl methacrylic hydroxide, 2-trimethylammoniumacrylic hydroxide, 2-trimethylammonium-methyl methacrylic chloride, 2-trimethylammonium-methylacrylic chloride, 2-
- 10 methacryloyloxyethyltrimethyl-ammonium methyl sulfate and 2-hydroxy-3-methacroyloxy-propyltrimethylammonium chloride.

Where the polymer is intended to be used for manufacturing a contact lens, it is preferred that the anionic-cationic monomer pair be either a conjugate of an

15 ethylenically unsaturated weak acid and an ethylenically unsaturated weak base or an ethylenically unsaturated strong acid and ethylenically unsaturated strong base. Where it is not possible to form these conjugate monomer pairs by direct reaction of the acid monomer with the base

20 monomer, the conjugates can usually be prepared from the salts of the acids, e.g., the silver and barium salts, and the halides of the bases, e.g., the chlorides, bromides and iodides, by means of the disproportionation reaction.

While cationic-anionic monomer pairs based on

25 conjugates of a strong acid and a weak base or conjugates of a weak acid and a strong base can be used, the dimensional stability of the resulting hydrogel may be more sensitive to changes in Ph than might be desirable for some applications, particularly, contact lenses. However, for

30 applications where dimensional stability is not important,

35

SUBSTITUTE SHEET

1

-7-

5 e.g., drug delivery compositions, such monomer pairs are entirely suitable.

Included within the expression "cationic-anionic monomer pair" or its equivalent "conjugate monomer pair" as used herein are ethylenically unsaturated internal salts containing positive and negative charges substantially in balance with each other. Examples of these internal monomeric salts which can be used herein as the cationic-anionic monomer pair are N-(3-sulfopropyl)-methacryloxyethyl-N,N-dimethylammonium-betain (SPE), N-(3-sulfo-
10 propyl)-N-methacrylamidopropyl-N,N-dimethylammonium-betain (SPP), 1-(3-sulfopropyl)-2-vinyl-pyridinium-betain (SPV), N-(3-carboxypropyl)-N-methylamino-methacryloyloxyethyl-N,N-dimethylammonium-betain (CPE), N-(3-carboxypropyl) aminoethylmethacrylate, 2-(methacryloyloxy)ethyl-2-
15 (trimethylammonium) ethylphosphate, etc.

Following its preparation, the cationic-anionic monomer pair is combined with at least one ethylenically unsaturated non-ionic monomer which can be hydrophilic, e.g., 2-hydroxyethyl methacrylate (HEMA), hydroxy-
25 propylmethacrylate, vinylpyrrolidone, glycerylmethacrylate, acrylamide, etc., or hydrophobic, e.g., silicone-acrylate, silicone-alkylacrylate, silicone-alkylmethacrylate, fluoromethacrylate, fluorosilico-methacrylate, etc. The amount of non-ionic monomer(s) can vary from about 1 to
30 about 99.5, and preferably from about 50 to about 95, weight percent of the total weight of monomer present in

35

SUBSTITUTE SHEET

1

-8-

5 the polymer-forming composition. Where the polymer-forming composition contains only hydrophilic non-ionic monomer(s), the amount of such monomer(s) can vary from about 50 to about 99.5, and preferably from about 65 to about 95, weight percent of the total monomer content. Where the
10 polymer-forming composition contains only hydrophobic non-ionic monomer(s), the amount of such monomers can vary from about 0.5 to about 80, and preferably from about 1 to about 60, weight percent of the total monomer content. Combinations of hydrophilic and hydrophobic monomers over a
15 wide range of weight ratios can be utilized to impart a variety of mechanical and/or water swellability performance characteristics.

The order of addition of the monomer components to the polymer-forming composition is generally not
20 critical. However, it is preferred to combine both components of the cationic-anionic monomer pair before adding any of the other ingredients of the polymerization medium since this will provide better control over the balanced conjugate-forming operation.

25 The foregoing monomer mixture can also contain a crosslinking monomer containing at least two ethylenic sites. Examples of such crosslinking monomers include ethylene glycol dimethacrylate (EGDMA) and diacrylate, diethyleneglycol dimethacrylate and diacrylate,
30 triethyleneglycol dimethacrylate and diacrylate, 1,3-propanediol dimethacrylate and diacrylate, 2,2-

35

SUBSTITUTE SHEET

1

-9-

5 dimethylpropanediol diacrylate, tripropylene glycol
dimethacrylate and diacrylate, 1,3-butylene glycol
dimethacrylate and diacrylate, divinylbenzene, sorbitol
dimethacrylate, bis-acrylamide, etc. In general, the
crosslinking monomer can be present at a level of from
10 about 0.01 to about 5, and preferably from about 0.2 to
about 2, weight percent of the total weight of monomers
present in the polymer-forming mixture.

In lieu of crosslinking monomer, covalent
crosslinking of the non-hydrated polymer of this invention
15 can be achieved by other means, e.g., by heating the
polymer prior to hydration, e.g., at 100-150°C, so that
ionic bonds in at least some carboxyl-amine conjugates are
converted to amidic bonds. Crosslinking can also be
achieved by irradiating the non-hydrated polymer, e.g., at
20 from 0.1 to 1.0 megarads. As those skilled in the art
recognize, whichever of these methods is used the degree of
crosslinking must be sufficient to render the polymer water
soluble yet water swellable.

Polymerization of the monomer mixture should be
25 carried out in the absence of water. However, the monomer
mixture can be diluted with suitable non-aqueous solvents,
e.g., glycerine, ethylene glycol, propylene glycol,
diacetin, acetic acid, dimethylsulfoxide,
dimethylformamide, the cellosolves, etc., to control volume
30 changes during xerogel lens swelling. The monomer mixture

35

SUBSTITUTE SHEET

1

-10-

5 including any other ingredients such as crosslinking monomer, peroxide initiator, etc., can be polymerized to provide the balanced charge polymer of this invention employing known and conventional techniques. The polymer can be formed in situ in a suitable mold via the spin
10 casting procedure to provide a hydrophilic contact lens. Suitable spin casting apparatus and techniques are disclosed, inter alia, in U.S. Patent Nos. 3,660,545, 4,468,184, 4,516,924, 4,517,138, 4,517,139, 4,517,140 and 4,680,149, the contents of which are incorporated by
15 reference herein. The polymer can also be formed in situ in a two-piece lens mold to provide the desired lens shape. Alternatively, a contact lens can be obtained by lathing a lens blank fabricated from the balanced charge polymer to the appropriate configuration.

20 In addition to contact lenses, the balanced charge polymer of this invention can be used to prepare implantable prostheses, e.g., intra-corneal implants, intra-ocular lenses, etc., drug delivery systems, and the like.

25 The following examples are illustrative of the balanced charge polymer of this invention and contact lenses fabricated therefrom.

30

35

SUBSTITUTE SHEET

1

-11-

5

EXAMPLE 1

This example compares the surface soiling characteristics of two contact lenses, Lenses A and B, prepared by molding in a two-piece plastic lens mold a polymer obtained in accordance with this invention (Lens A) and a known polymer (Lens B).

The polymer-forming compositions were formulated as follows:

Lens A

	<u>Component</u>	<u>Weight %</u>
15	N,N-Dimethylaminoethyl methacrylate	5.678
	Methacrylic acid (MAA)	2.822
	2-Hydroxyethyl methacrylate (HEMA)	76.075
	Ethylene glycol dimethacrylate (EGDMA)	0.425
	Ethylene glycol	15.0

20

Lens BComponent

	MAA	1.5
	HEMA	83.0
	EGDMA	0.5
	Glycerine	15

25

To each of these compositions was added 0.5 weight percent of azobisdimethylvaleronitrile initiator. A quantity of each polymer-forming composition was placed in a two-piece plastic lens mold where polymerization was carried out under nitrogen at 80°C for 5 hours to provide

30

35

SUBSTITUTE SHEET

-12-

1
5 the contact lens which was then hydrated in isotonic saline solution.

The 24 hour assay procedure whereby the hydrated lenses were measured for their tendency to attract protein, specifically lysozyme, to their surfaces was as follows:

10 Each lens was incubated at 35°C in a Ph 7.4 buffered isotonic saline solution containing 1.2 mg lysozyme/ml. After 24 hours of incubation, the lenses were rinsed with buffered saline and their ultraviolet absorbances were measured spectrophotometrically. Protein
15 deposition was calculated using an extinction coefficient of 2.38 cm³/mg at 280 nm.

In addition to the foregoing protein deposition assay, Lenses A and B were compared for pH sensitivity, tensile strength (g/mm²) and ionic charge sensitivity.

20 The results of all three testing procedures were as follows:

<u>Property</u>	<u>Lens A</u>	<u>Lens B</u>
25 Retention of Lysozyme on the Lens Surface	0.03 mg/lens (estimated)	0.33 mg/lens
pH Sensitivity	Not sensitive to pH 3.5-8.5; lens expounds 6% at pH 9 and expands 3% at pH 3.5.	Sensitive to different levels of pH; lens shrinks 10% at pH 4.

30

35

SUBSTITUTE SHEET

1

-13-

5	Tensile Strength (g/mm ²)	70	80
10	Ionic charge sensitivity	Not Sensitive; water content changes 2% between saline and deion- ized water	Very sensi- tive; water content chang s 15% between saline and deionized water

In addition to the dramatically reduced retention of lysozyme on its surfaces, Lens A exhibited greater biocompatibility, higher water affinity, reduced dehydration and greater wearer comfort than Lens B.

EXAMPLE 2

90 Weight parts of HEMA containing 0.4 weight percent of EGDMA was mixed with 10 weight parts of monomer charge-conjugate prepared in the following manner:

1 Mole of methacrylic acid was slowly added to 1 mole of dimethylaminoethyl methacrylate under intensive cooling and stirring so that the temperature would not exceed 30°C. The conjugate was recrystallized from methanol solution. 0.1 Weight percent of azobisisobutyronitrile initiator was added to the monomer mixture which was then polymerized at 60°C under nitrogen in a two-piece plastic mold. After 2 hours the mold was opened and the finished lens hydrated in isotonic saline solution. The liquid content of the lens was 55 weight percent.

35

SUBSTITUTE SHEET

-14-

5

EXAMPLE 3

The azobisisobutyronitrile initiator in the polymer-forming mixture of Example 2 was replaced with benzoin methylether and the mixture was polymerized by spincasting with UV irradiation (at 365 nm; 60 W Hg lamp at 5.0 cm distance for 20 minutes). The resulting lens had similar properties as the lens of Example 2.

EXAMPLE 4

50 Weight parts of ethyltriglycolmethacrylate, 50 weight parts of the monomer conjugate of Example 2 and 2 weight parts of EGDMA were mixed. Polymerization of the mixture was initiated with 0.5% of azobisdimethylvaleronitrile in a two-piece plastic mold at 60°C for 3 hours and at 80°C for 2 hours. The resulting lens contained 71 weight percent of water at equilibrium hydration in saline.

EXAMPLE 5

50 Grams of ethoxyethyl methacrylate were mixed with 50 grams of the monomer conjugate of Example 2 and 0.8 grams of EGDMA. The mixture was initiated by 0.08% of azobisisobutyronitrile and polymerized for 24 hours at 60°C in a sealed glass ampule. After cooling, the ampule was broken and the resulting polymer block was lathed and polished into a lens. The resulting lens contained 80 weight percent water after complete hydration in isotonic saline solution.

35

SUBSTITUTE SHEET

-15-

EXAMPLE 6

A mixture of 20 weight parts of 3-methacryloxypropyltris(trimethylsiloxy)silane, 1 weight part of EGDMA and 80 weight parts of the monomer conjugate of Example 2 was diluted with 10% of Cellosolve. 0.1 Weight percent of azobisisobutyronitrile was added and the mixture was polymerized in a plastic two-piece plastic mold at 80°C for 3 hours. The resulting lens contained 60 weight percent water after complete hydration in saline, an oxygen permeability of $DK=35-40 \times 10^{-11}$ (cm^2/sec) ($\text{ml O}_2/[\text{ml} \times \text{mmHg}]$) and a tensile strength in the hydrated state of 120g/mm².

EXAMPLE 7

30 Weight parts of n-hexyl methacrylate, 0.5 weight parts of EGDMA and 70 weight parts of the monomer conjugate of Example 2 were mixed. The mixture was initiated by 0.1 weight percent of azobisisobutyronitrile and polymerized 4 hours at 60°C in a two-piece plastic mold. The resulting lens contained 70 weight percent water after complete hydration in saline and exhibited a tensile strength in the hydrated state of 110g/mm².

EXAMPLE 8

30 Grams of ethylmethacrylate were mixed with 7 grams of the monomer conjugate of Example 2 and 0.5 grams of EGDMA. The mixture was initiated by 0.1 grams azobisisobutyronitrile and polymerized in a two-piece plastic mold at 80°C for 3 hours. The resulting lens

SUBSTITUTE SHEET

1

-16-

5 contained 78 weight percent water after complete hydration
in saline and a tensile strength of 100 g/mm².

EXAMPLE 9

80 Weight percent parts of hydroxypropyl
methacrylate, 20 weight parts of the monomer conjugated
10 from Example 2 and 0.5 parts EGDMA were mixed. 0.1 Weight
percent azobisisobutyronitrile two-piece plastic mold was
added and the mixture was polymerized at 75°C for 4 hours.
The resulting lens contained 57 weight percent water after
complete hydration in saline, a tensile strength of 80
15 g/mm² and an elongation in the hydrated state of 440%.

EXAMPLE 10

30 Grams of methyl methacrylate were mixed with
70 grams of the monomer conjugate of Example 2 together
with 0.5 grams EGDMA. Polymerization was initiated by
20 0.08% weight percent of azobisisobutyronitrile for 24 hours
at 60°C in a sealed glass ampule. After cooling, the
ampule was broken and the resulting polymer block was
lathed and polished into a lens. The resulting lens
contained 70 weight percent water after complete hydration
25 in isotonic saline.

EXAMPLE 11

3 Weight parts of tertiary-butylmethacrylate, 0.05
weight parts of EGDMA and 7 weight parts of the monomer
conjugate of Example 2 were mixed. The mixture was
30 initiated with 0.5% azobisdimethylvaleronitrile and

35

SUBSTITUTE SHEET

1

-17-

5 polymerized in a two-piece plastic mold at 60°C for 3 hours. The resulting lens contained 77 weight percent water after hydration in saline and a tensile strength in the hydrated state of 80 g/mm².

EXAMPLE 12

10 3 Weight parts of n-butylmethacrylate, 7 weight parts of the monomer conjugate of Example 2 and 0.05 weight parts of EGDMA were mixed. The mixture was initiated with 0.5% azobisdimethylvaleronitrile and polymerized in a two-part plastic mold at 60°C for 4 hours. The resulting lens
15 contained 70 weight percent water after complete hydration in saline.

EXAMPLE 13

3 Weight parts of tetrafluoropropylmethacrylate, 7 weight parts of the monomer conjugate of Example 2 and
20 0.05 weight of EGDMA were mixed. Polymerization was initiated with azobisdimethylvaleronitrile in a two-piece plastic mold at 80°C for 3 hours. The resulting lens contained 70 weight percent water after complete hydration in saline.

EXAMPLE 14

25 1 Mole of methacrylic acid was slowly added to 1 mole dimethylaminoethylmethacrylamide and cooled below 20°C. 20 weight parts of the resulting conjugate were mixed with 80 weight parts of HEMA and 0.2 weight parts of
30 EGDMA. Polymerization was initiated with 0.5 weight

35

1

-18-

5 percent of azobisdimethylvaleronitrile in substantially the same manner as in Example 13. The resulting lens contained 69 weight percent water after complete full hydration in isotonic saline.

EXAMPLE 15

10 10 Weight parts of methacryloyloxypropyl sulfonic acid and methacryloyloxypropyl trimethylammonium base conjugate were dissolved in 90 weight parts of HEMA containing 0.5 weight percent of EGDMA. Polymerization of the mixture was initiated by 0.5 weight percent of
15 azobisdimethyl-valeronitrile in substantially the same manner as in Example 13. The resulting lens had 50% of water after complete hydration in isotonic saline solution.

EXAMPLE 16

20 10.1 Weight parts of SPE were dissolved in 15 weight parts of propyleneglycol and 74.4 weight parts of HEMA containing 0.5 weight percent EGDMA. Polymerization was initiated by 0.2 weight percent benzoinmethylether. A contact lens was manufactured from the polymer-forming mixture by the spincasting method employing
25 photopolymerization. The resulting lens contained 52 weight percent water in isotonic saline solution.

EXAMPLE 17

A conjugate monomer pair was prepared by slowly combining 8.46g t-butylaminoethylmethacrylate (t-BAEMA) in
30 10g acetone with 4.3g methacrylic acid (MAA) in 10g acetone

35

SUBSTITUTE SHEET

1

-19-

5 and thereafter cooling the combined material to below 5°C.
The crude t-BAEMA-MAA conjugate pair was separated from the
acetone by filtration, dried at ambient temperature under
vacuum and recrystallized by dissolving 10g of the
conjugate in 15g acetone at 35°C and placing the solution
10 overnight in a refrigerator.

A contact lens was prepared by combining 1.6g
HEMA, 0.4g t-BAEMA-MAA conjugate pair prepared as
described, 0.01 azobisdimethylvaleronitrile and 0.35g
propylene glycol (solvent), placing the polymer-forming
15 composition in a two-piece plastic lens mold and
polymerizing as in Example 1. The resulting contact lens
swelled 55 weight percent in isotonic saline solution.

EXAMPLE 18

Following the procedures described in Example 17,
20 a contact lens was prepared from a polymer-forming
composition containing 1.7g hydroxypropylmethacrylate, 0.3
g N-methacryloyoxyethyl-N,N-dimethyl-N,2-ethyl
carboxybetaine (CPE), 0.01 g EGDMA and 0.01g
azobisdimethylvaleronitrile. The resulting contact lens
25 was clear and swelled to 51 weight percent of water in
isotonic saline solution.

30

35

SUBSTITUTE SHEET

1

-20-

5 WHAT IS CLAIMED IS:

1. A charge balanced, water swellable crosslinked polymer which comprises the polymerizate derived from the copolymerization of at least one cationic-anionic pair of ethylenically unsaturated monomers and at
10 least one non-ionic ethylenically unsaturated monomer.

2. The polymer of Claim 1 wherein the polymerizate is further derived from a crosslinking monomer containing at least two ethylenic sites.

3. The polymer of Claim 1 wherein the cationic-anionic pair is made up of a relatively weak monomeric acid
15 and a relatively weak monomer base.

4. The polymer of Claim 3 wherein the relatively weak monomeric acid is a carboxylic acid and the relatively weak base is a primary, secondary or tertiary amine.

5. The polymer of Claim 4 wherein the carboxylic acid is selected from the group consisting of acrylic acid, methacrylic acid, itaconic and, maleic acid, 2-vinylpropionic acid and 4-vinylpropionic acid and the
20 primary, secondary or tertiary amine is selected from aminoethylmethacrylate, methylaminoethylmethacrylate, N,N-dimethylaminoethyl-methacrylate, N,N-diethanolaminoethylmethacrylate, N,N-dimethoxyethylaminoethylmethacrylate, vinyl amine, aminostyrene, 2-vinyl pyridine, 4-vinyl pyridine,
25 morpholinomethacrylate and N-(2-vinyloxyethyl) piperidine.
30

35

SUBSTITUTE SHEET

1

-21-

5 6. The polymer of Claim 1 wherein the cationic-anionic pair is made up of a relatively strong monomeric acid and a relatively strong monomeric base.

7. The polymer of Claim 6 wherein the relatively strong monomeric acid is a sulfonic acid and the relatively strong base is a quaternary ammonium compound.

8. The polymer of Claim 7 wherein the sulfonic acid is selected from the group consisting of methacryloyloxypropyl-sulfonic acid, vinylsulfonic acid and p-styrenesulfonic acid and the quaternary ammonium compound is selected from the group consisting of 2-trimethylammonium methyl methacrylic hydroxide, 2-trimethylammonium-acrylic hydroxide, 2-trimethylammonium methyl methacrylic chloride, 2-trimethylammonium methyl methacrylic chloride, 2-methacryloyloxyethyltrimethyl-ammonium methyl sulfate and 2-hydroxy-3-methacryloyloxypropyltrimethylammonium chloride.

9. The polymer of Claim 1 wherein the cationic-anionic pair is made up of a relatively strong acid and a relatively weak base.

10. The polymer of Claim 1 wherein the cationic-anionic pair is made up of a relatively weak acid and a relatively strong base.

11. The polymer of Claim 1 wherein the cationic-anionic pair is provided as an internal monomeric salt.

12. The polymer of Claim 11 wherein the internal monomeric salt is selected from the group consisting of

35

SUBSTITUTE SHEET

1

-22-

- 5 N-(3-sulfopropyl)-methacroyloxyethyl-N,N-dimethylammonium-
betain, N-(3-sulfo-propyl)-N-methacrylamidopropyl-N, N-
dimethylammonium-betain, 1-(3-sulfopropyl)-2-vinyl-
pyridinium-betain, N-methacryloyloxyethyl-N,N-dimethyl-N,2-
ethyl carboxybetaine (CPE), N-(3-carboxypropyl)-N-
10 methylamino-ethylmethacrylate, N-(3-carboxypropyl)
aminoethylmethacrylate and 2-(methacryloyloxy)ethyl-2-
(trimethylammonium) ethylphosphate.

13. The polymer of Claim 1 wherein the non-ionic
monomer is selected from the group consisting of 2-
15 hydroxyethyl methacrylate, hydroxypropylmethacrylate,
vinylpyrrolidone, glycerylmethacrylate, acrylamide,
silicone-acrylate, silicone-alkylacrylate, silicone-
alkylmethacrylate, fluoromethacrylate, fluorosilico-
methacrylate and mixtures thereof.

- 20 14. A hydrophilic contact lens manufactured from
the polymer of Claim 1.

15. A hydrophilic contact lens manufactured from
the polymer of Claim 2.

- 25 16. A hydrophilic contact lens manufactured from
the polymer of Claim 3.

17. A hydrophilic contact lens manufactured from
the polymer of Claim 4.

18. A hydrophilic contact lens manufactured from
the polymer of Claim 5.

- 30 19. A hydrophilic contact lens manufactured from
the polymer of Claim 6.

35

SUBSTITUTE SHEET

1

-23-

5 20. A hydrophilic contact lens manufactured from
the polymer of Claim 7.

 21. A hydrophilic contact lens manufactured from
the polymer of Claim 8.

10 22. A hydrophilic contact lens manufactured from
the polymer of Claim 11.

 23. A hydrophilic contact lens manufactured from
the polymer of Claim 12.

 24. A hydrophilic contact lens manufactured from
the polymer of Claim 13.

15

20

25

30

35

SUBSTITUTE SHEET

INTERNATIONAL SEARCH REPORT

PCT/US91/09625

International Application No.

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)¹

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC (5): C08F 220/06, 228/02, 236/02; G02C 7/04

U.S. CL. 526/265, 278, 287, 288, 310, 312; 351/160R, 160H

II. FIELDS SEARCHED

Minimum Documentation Searched *

Classification System	Classification Symbols
U.S.	526/265, 278, 287, 288, 310, 312; 351/160R, 160H

Documentation Searched other than Minimum Documentation
to the Extent that such Documents are Included in the Fields Searched *

III. DOCUMENTS CONSIDERED TO BE RELEVANT^{1,2}

Category *	Citation of Document, ^{1,2} with indication, where appropriate, of the relevant passages ^{1,2}	Relevant to Claim No. ^{1,2}
E, X	US, A, 5,075,399 (AHMED ET AL.) 24 DECEMBER 1991; See entire document.	1-24
Y	US, A, 4,666,964 (HUNTER ET AL.) 19 MAY 1987; See entire document.	1-24
Y	US, A, 4,251,651 (KAWAKAMI ET AL.) 17 FEBRUARY 1981; See entire document.	1-24

* Special categories of cited documents: ^{1,2}

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search ¹

16 MARCH 1992

International Searching Authority ¹

ISA/US

Date of Mailing of this International Search Report ¹

16 APR 1992

Signature of Authorizing Officer ¹

Paul Michl
Paul Michl

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers _____, because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim numbers _____, because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim numbers _____, because they are dependent claims not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☒ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This International Searching Authority found multiple inventions in this international application as follows:

Group I: Claims 1-13 drawn to ampholytic polymer compositions, classified in Class 526, Subclass 287
 Group II: Claims 14-24 drawn to lenses from polymer compositions of Group I, Classified in Class 351, Subclass 160R.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application. Telephone Practice
 2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
 3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
 4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.
- Remark on Protest
- ☐ The additional search fees were accompanied by applicant's protest.
 - ☐ No protest accompanied the payment of additional search fees.

